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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61M 37/00, A61N 1/30 — A1

(11) International Publication Number: **WO 99/29365**

(43) International Publication Date: 17 June 1999 (17.06.99)

(21) International Application Number: PCT/US98/26203

(22) International Filing Date: 9 December 1998 (09.12.98)

(30) Priority Data:

60/069,339	11 December 1997 (11.12.97)	US
60/069,340	11 December 1997 (11.12.97)	US

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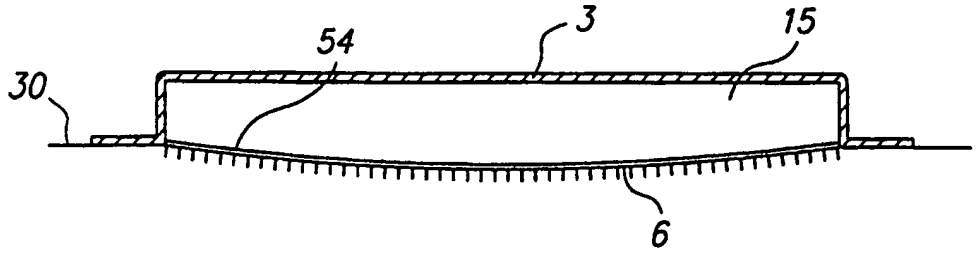
(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: DEVICE FOR ENHANCING TRANSDERMAL AGENT FLUX



(57) Abstract

A device (3) comprising a sheet member (6) having a plurality of microprotrusions (4) for penetrating the skin and a substantially incompressible agent reservoir housing (15) contacting and extending across the sheet member (6) for transmitting a hold–down force applied the sheet member (6) to maintain the microprotrusions (4) in skin–piercing relation to the skin, even during and after normal patient body movement.

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DEVICE FOR ENHANCING TRANSDERMAL AGENT FLUX

TECHNICAL FIELD

The present invention relates to transdermal agent delivery and sampling. More particularly, this invention relates to the transdermal delivery of agents, such as peptides and proteins, through the skin, as well as the transdermal sampling of agents from the body, such as glucose, other body analytes and substances of abuse, such as alcohol and illicit drugs.

BACKGROUND ART

Interest in the transdermal delivery of high molecular weight beneficial agents such as peptides, proteins and oligonucleotides to the human body continues to grow with the increasing number of medically useful peptides, proteins and oligonucleotides becoming available in large quantities and pure form. The transdermal delivery of peptides, proteins and oligonucleotides still faces significant problems. In many instances, the rate of delivery or flux of such agents through the skin is insufficient to produce a desired therapeutic effect due to their large size/molecular weight and the resulting inability to pass through natural pathways (pores, hair follicles, etc.) through skin. In addition, polypeptides and proteins are easily degradable during penetration of the skin, prior to reaching target cells. Likewise, the passive flux of water soluble small (e.g., 200 to 500 dalton) agent molecules is often limited.

One method of increasing the transdermal delivery of agents relies on the application of an electric current across the body surface or on "electrotransport". "Electrotransport" refers generally to the passage of a beneficial agent, e.g., a drug or drug precursor, through a body surface such as skin, mucous membranes, nails, and the like. The transport of the agent

is induced or enhanced by the application of an electrical potential, which results in the application of electric current, which delivers or enhances delivery of the agent. The electrotransport of agents through a body surface may be attained in various manners. One widely used electrotransport process, iontophoresis, involves the electrically induced transport of charged ions. Electroosmosis, another type of electrotransport process, involves the movement of a solvent with the agent through a membrane under the influence of an electric field. Electroporation, still another type of electrotransport, involves the passage of an agent through pores formed by applying a high voltage electrical pulse to a membrane. In many instances, more than one of these processes may be occurring simultaneously to different extents. Accordingly, the term "electrotransport" is given herein its broadest possible interpretation, to include the electrically induced or enhanced transport of at least one charged or uncharged agent, or mixtures thereof, regardless of the specific mechanism(s) by which the agent is actually being transported. Electrotransport delivery generally increases agent delivery, particularly large molecular weight species (e.g., polypeptides) delivery rates, relative to passive or non-electrically assisted transdermal delivery. However, further increases in transdermal delivery rates and reductions in polypeptide degradation during transdermal delivery are highly desirable.

One method of increasing the agent transdermal delivery rate involves pre-treating the skin with, or co-delivering with the beneficial agent, a skin permeation enhancer. The term "permeation enhancer" is broadly used herein to describe a substance which, when applied to a body surface through which the agent is delivered, enhances its flux therethrough. The mechanism may involve a reduction of the electrical resistance of the body surface to the passage of the agent therethrough, an increase in the permselectivity and/or permeability of the body surface, the creation of hydrophilic pathways through the body surface, and/or a reduction in the degradation of the agent (e.g., degradation by skin enzymes) during

electrotransport.

There have also been many attempts to mechanically disrupt the skin in order to enhance transdermal flux, such as, U.S. Patent Nos. 3,814,097 issued to Ganderton et al., 5,279,544 issued to Gross et al., 5,250,023 issued to Lee et al., 3,964,482 issued to Gerstel et al., U.S. Patent No. Re 25,637 issued to Kravitz et al. and PCT application WO 96/37155. These devices typically utilize tubular or cylindrical structures generally, although Gerstel does disclose the use of other shapes, to pierce the outer layer of the skin. The piercing elements disclosed in these references generally extend perpendicular from a thin flat member, such as a pad or metal sheet.

More recently, attempts have been made to anchor the tiny piercing elements of such devices in the skin in order to keep the drug transmitting pathways open, which pathways are cut through the stratum corneum by the microprotrusions. See for example, Cormier, et al., WO 97/48440. Unfortunately, because of the extremely small size of the microprotrusions, the formation of barbs and similar anchoring elements on the microprotrusions is problematic.

The microprotrusion arrays disclosed in WO 97/48440 are in the form of a thin metal sheet having a plurality of agent-transmitting openings therethrough. The sheet has a skin proximal surface and a skin distal surface. A plurality of etched and punched mircroprotrusions extend roughly perpendicularly from the skin distal surface of the sheet. A reservoir adapted to contain (in the case of agent delivery) or receive (in the case of agent sampling) the agent is positioned on the skin distal surface of the sheet. The microprotrusion array and the agent reservoir are then pressed onto the skin surface and maintained on the skin using an adhesive overlay or similar securing means as shown in Figure 1. Thus, the sheet member 6 having the microprotrusions 4 extending from a skin distal surface thereof is placed on the skin with the microprotrusions 4 penetrating into the skin surface. The agent reservoir 27 is shown on the skin distal side of sheet 6. The structure

is held in place on the skin 30 by an overlay 3 having adhesive coated on at least the peripheral surfaces 9 thereof.

The agent reservoir 27 in the Figure 1 device tended to be composed of soft compliant materials such as gels. Such soft compliant, and even flowable, materials were preferred with sheet member 6 since the gel material could easily flow into the openings of sheet member 6 in order to come into direct contact with skin 30.

DESCRIPTION OF THE INVENTION

Unfortunately, when using structures such as that disclosed in Figure 1, it was found that with normal patient body movement, the microprotrusions 4 eventually worked their way out of the skin 30, as shown in Figure 2, thereby allowing the pathways cut through the stratum corneum to quickly heal and eventually close, making further agent delivery therethrough problematic. In part, the compressibility of the agent reservoir 27 contributed to this problem.

The present invention provides a device suitable for increasing transdermal flux. The device has microprotrusions which penetrate a body surface (e.g., skin) to enhance agent delivery or sampling. The device of the present invention is useful for introducing an aqent (e.g., a drug) into, or withdrawing an agent (e.g., a body analyte) from a body surface such as skin. The device includes a body surface piercing member having a plurality of microprotrusions which extend from a body surface proximal portion of the member. The microprotrusions are adapted to pierce the body surface to a depth of up to about 500 μm. Thus, when applied to the skin, the microprotrusions are adapted to at least pierce through the stratum corneum layer. The device further includes a housing which contains a reservoir for the agent to be delivered or sampled. The housing is either a separate element which contacts the piercing member, or is integral with the piercing member, and maintains the reservoir in agent-transmitting relation with the

pierced body surface. The housing is characterized by having a compressibility, in a direction normal to the body surface, of less than about 250 μm. The device further includes a securing member for securing the device to the body surface.

In one aspect of the invention, the piercing member and the housing are separate elements. The piercing member comprises a thin sheet having a plurality of openings therethrough for transport of the agent therethrough. The sheet has a body proximal surface which is adapted to be placed against the body surface, said plurality of microprotrusions extending from the body proximal surface. The housing is adapted to extend across at least a portion, and preferably the entire, body distal surface of the sheet.

In another aspect of the invention, the piercing member comprises a thin sheet having a body proximal edge, with said plurality of microprotrusions adapted to be placed against said body surface. The plane of the sheet is oriented in roughly perpendicular relation to the body surface being pierced. The housing is comprising of a plurality of said sheets, fastened together in spaced apart relation, in order to create reservoir containing voids between the adjacent sheets.

Preferably, the housing has a compressibility, in a direction normal to the body surface being pierced, of less than about 50 μm. Most preferably, the housing is comprised of porous sintered high density polyethylene or an open cell polyurethane foam having a compressibility of less than about 25 μm and a void volume of about 10 to 60%.

The device of the present invention can be used in connection with agent delivery, agent sampling or both. In particular, the device of the present invention is used in connection with transdermal drug delivery, transdermal analyte sampling, or both. Delivery devices for use with the present invention include, but are not limited to, electrotransport devices, passive devices, osmotic devices and pressure driven devices. Sampling devices for use with the present invention include, but are not limited to, reverse electrotransport devices, passive devices, negative pressure driven,

and osmotic devices.

BRIEF DESCRIPTION OF THE DRAWINGS

In the figures, like reference numerals refer to like elements in the several drawings.

Figure 1 is a cross-sectional view of a prior art device at the time of skin penetration;

Figure 2 is the device of Figure 1 at a later point in time showing microprotrusion withdrawal from the body surface;

Figure 3 is an enlarged cross-sectional view of an incompressible reservoir housing and skin penetrating member of the present invention taken along line III-III in Figure 4;

Figure 4 is a top plan view of the device of Figure 3, with the securing overlay removed for ease of illustration;

Figure 5 is an enlarged perspective view of the bottom side of a skin penetrating member in accordance with one embodiment of the present invention;

Figures 6, 8 and 9 are top plan views of other embodiments of the incompressible housing and skin penetrating member, with the securing overlay removed for ease of illustration;

Figure 7 is an exploded perspective view of an integral incompressible housing and skin penetrating member with a securing overlay;

Figure 10 is a side view of another embodiment of an incompressible reservoir housing and skin penetrating member in accordance with the present invention;

Figure 11 is a top view of still another embodiment of the incompressible reservoir housing of the present invention with the securing overlay removed for ease of illustration;

Figure 12 is a perspective view of yet another embodiment of the incompressible reservoir housing of the present invention;

Figure 13 is a perspective view of still another embodiment of the incompressible reservoir housing of the present invention;

Figure 14 is a perspective view of a preferred incompressible reservoir housing in accordance with another embodiment of the present invention;

Figure 15 is an exploded perspective view of an electrotransport agent delivery/sampling system according to one embodiment of the present invention;

Figure 16 is a bottom plan view of the electrotransport agent delivery/sampling system of Figure 15;

Figure 17 is a right side elevational view of the electrotransport agent delivery/sampling system of Figure 15;

Figure 18 is a rear elevational view of the electrotransport agent delivery/sampling system of Figure 15;

Figure 19 is a cross-sectional view taken along line 19-19 of the electrotransport agent delivery/sampling system of Figure 17;

Figure 20 is a diagrammatic cross-sectional view of a passive agent delivery/sampling system in accordance with one embodiment of the present invention;

Figure 21 is an exploded perspective view of another integral incompressible reservoir housing and skin penetrating member;

Figure 22 is a graph showing the percent pathways dyed one hour after application of microprotrusion arrays into the skin of living hairless guinea pigs;

Figure 23 is a graph showing pathway shutdown as a function of time after application of microprotrusion arrays into the skin of living hairless guinea pigs; and

Figure 24 is another graph showing pathway shutdown as a function of time after application of microprotrusion arrays into the skin of living hairless guinea pigs.

MODES FOR CARRYING OUT THE INVENTION

Turning now to the drawings in detail, the device 2 of the present invention is generally shown in Figure 3 comprising skin penetrating sheet member 6 and housing 15. Device 2 is used to enhance the transdermal delivery or sampling of an agent. The terms "substance", "agent" and "drug" are used interchangeably herein and broadly include physiologically or pharmacologically active substances for producing a localized or systemic effect or effects in mammals including humans and primates, avians, valuable domestic household, sport or farm animals, or for administering to

laboratory animals such as mice, rats, guinea pigs, and the like. These terms also include substances such as glucose, other body analytes that are found in the tissue, interstitial fluid and/or blood, alcohol, licit substances, and illicit drugs, etc. that can be sampled through the skin.

The major barrier to the transdermal flux of agents (e.g., drugs to be delivered and analytes to be sampled) is the outermost layer of the skin (i.e., stratum corneum). The inner division of the epidermis generally comprises three layers commonly identified as stratum granulosum, stratum malpighii, and stratum germinativum. There is essentially little or no resistance to transport or to absorption of an agent through the stratum granulosum, stratum malpighii, and stratum germinativum. Device 2 comprises a rigid support member 15 and a compliant sheet member 6 (see Figure 5 in which device 2 is in an inverted position to show the microprotrusions) having a plurality of microprotrusions 4 extending outwardly therefrom. The device 2 is pressed against an area of skin through which an agent is to be transdermally delivered or sampled. The microprotrusions 4 form tiny slits in the skin and penetrate at least through the stratum corneum so that the agent is conducted through the skin with little or no resistance. Typically, the microprotrusions penetrate the skin to a depth of up to 500 μm, more typically to a depth of 50 to 300 μm. The microprotrusions 4 can be microblades (Figures 3 and 5), pins (not shown), or any of a variety of configurations for piercing the skin or body surface. The microprotrusions 4 penetrate the stratum corneum of the epidermis when pressure is applied to the top (i.e., skin distal side) of the housing 15 to increase the administration of, or sampling of, an agent through a body surface. The term "body surface" as used herein refers generally to the skin, mucous membranes, and nails of an animal or human, and to the outer surface of a plant. The microprotrusions 4 penetrate the body surface to create good agent conduction from the system into the body, or vice versa.

In the embodiments shown in Figures 3-5, the sheet member 6 is formed with a plurality of openings 8, each opening 8 having at least one

microprotrusion 4 along the periphery thereof. The microprotrusions 4 cut microslits in the stratum corneum, thereby enhancing the transdermal flux of agent released from, or collected in, the agent containing or collecting reservoirs 27 housed by the plurality of voids 7.

Sheet member 6 can be composed of metal, silicon or plastic, although metals such as stainless steel and titanium are preferred. Sheet member 6 is generally compliant and flexible because of its relatively thin thickness. For example, when sheet member 6 is comprised of a metal such as stainless steel or titanium, the sheet member 6 will typically have a thickness of only about 5 μm to about 100 μm, and more typically about 25 μm to about 50 μm.

In accordance with the present invention, a substantially incompressible housing 15 is placed across the sheet member 6 (Figures 3 and 4). The housing 15 is then secured to the body surface with an adhesive securing overlay 3. The overlay 3 (Figures 7 and 10) is comprised of a sheet material which covers the housing 15 and extends beyond the peripheral edge of the housing 15 in order to make contact with the patient's skin 30. The device 2 is typically applied to the skin by pressing the device 2 into the skin, causing the tissue to become displaced. In this condition, the peripheral edge of overlay 3 is adhered to the surface 30 of the skin surrounding device 2. Then the manually applied pressure is released causing the skin and underlying tissue to return partially to its original state. However, the overlay 3 holds the housing 15 tightly against the skin 30 causing the skin 30 to be in a partially displaced state, as best shown in Figure 10. Because the housing 15 is substantially incompressible, the microprotrusions 4 are maintained in piercing relation with the body surface, even during normal patient movement. Thus, using the incompressible housing 15, the problem of prior art devices, namely the gradual withdrawal of the microprotrusions 4 from the skin as shown in Figure 2, is avoided. Because the reservoir housing 15 is substantially incompressible, a secure hold down force can be applied by the securing overlay 3 without causing

the agent reservoir material, which is typically comprised of a viscous liquid, gel or similar semisolid/soft material, to flow or otherwise deform thereby allowing protrusions 4 to withdraw from the skin as was the tendency with the prior art devices (Figures 1 and 2).

Housing 15 can be a variety of configurations, for example but not limited to the embodiments shown in Figures 3, 4, and 6-14. In the embodiment shown in Figures 3 and 4, housing 15 is an incompressible structure which forms a plurality of voids 7, extending through the thickness of the support member, which voids 7 collectively house reservoir 27 (Figure 3) for containing the agent that is to be delivered or for receiving the agent that is to be sampled. Between the voids 7 are a plurality of supports or cross-members 5 which are in contact with and extend across the width or length of the sheet member 6. The cross-members 5 transmit the hold-down force that is applied to the top of the housing 15 by the overlay 3. When used with a transdermal electrotransport device, the sheet member 6 and/or housing 15 are preferably electrically isolated or insulated from the current conducting elements (e.g., the electrodes) of the electrotransport device in order to avoid short circuiting the drug reservoir. This can be achieved by using electrically insulative materials or coatings for sheet member 6 and/or housing 15.

The overlay 3 may be made of a sheet material which is either elastic or inelastic. Examples of inelastic sheet materials include polyethylene terephthalate films and other fabric reinforced polymer films. An example of an elastic overlay is Medpar™. Elastic overlay sheet materials are preferred.

As used herein, the term "incompressible" when referring to housing 15 means that the housing 15 is compressed to only a small degree in a direction normal to the skin surface, by the hold down force applied by the securing overlay 3. Preferably, the housing 15 compresses a distance of less than 250 μm, and more preferably less than 50 μm, when the hold down forced is applied by the securing overlay 3.

The housing 15 maybe made from any material having the aforementioned low compressibility. Suitable materials include metals, metal alloys, ceramics, glasses, incompressible plastics, incompressible polymeric foams, and incompressible reinforced (e.g., carbon fiber reinforced) polymers. A particularly preferred incompressible housing material is a porous sintered high density polyethylene sold under the tradename Porex® by Porex Technologies, Inc., of Fairburn, GA.

The housing 15 may be either rigid or flexible, but preferably is flexible so that it more easily conforms to a patient body surface (e.g., the skin on a patient's arm). Preferably, when the housing 15 has a flat skin proximal surface, the housing 15 has the ability to flex into a curved configuration in response to the hold down force applied by the overlay 3. Most preferably, the housing 15 flexes (in response to the applied hold down force) to a degree such that the skin proximal surface of the housing 15 has a radius of curvature of less than about 10 cm. Alternatively, the housing can be arranged in individual rigid sections, adjacent sections being hingedly attached to one another.

Various embodiments of the reservoir housing 15 are illustrated in Figures 3-4 and 6-14. In the embodiments shown in Figures 3-4, 6-9 and 15, the housing 15 is comprised of a peripheral (e.g., annular) wall 53 having at least one cross-member 5 extending across the support member 15 so as to create a plurality of voids 7 which house the reservoir for the agent and to transmit the applied hold-down force substantially evenly across the sheet member 6 and without compressing the housing 15. The cross-members generally extend diagonally in Figures 6, 8 and 15 across the volume bounded by the outer wall of the housing 15. Diagonal, as used herein, is meant to describe embodiments other than cross-members joining two vertices of a rectilinear figure that are nonadjacent or passing through two nonadjacent edges of a polyhedron, as is apparent from the embodiments shown in the figures. As can be seen, the cross-members include oblique (Figure 8) and non-oblique (Figure 9) cross-members as well

as honeycomb configurations (Figure 4). The number of cross-members depends on a variety of factors, for example, the relative structural integrity or flexibility of the sheet member 6 and the housing 15, the distance across the housing 15, the size of the agent reservoir skin-contact area, and the volume of the agent reservoir. In general, when using sheet member 6 formed of very thin metal, the maximum distance between adjacent cross-members 5 in housing 15 will be no more than about 4 times, and preferably no more than about 2 times, the distance between adjacent microprotrusions 4 in sheet member 6. Figure 9 illustrates that the housing 15 can be comprised of a plurality of inner annular walls 55 connected by the cross-members 5 to the outer annular wall 53.

Figure 7 illustrates an alternate embodiment of the sheet member 6 wherein the microprotrusions 4 extend outwardly from a body contacting edge 49 of a thin, sheet member 6. In this embodiment, the plane of the sheet member 6 is oriented in approximately perpendicular relation to the body surface during use. The sheet member 6 has a spiral configuration which defines voids 51 for holding an agent-containing or an agent-receiving reservoir (not shown in Figure 7). Coiling, folding (not shown), and curving (not shown) as well as other forms of forming the sheet member 6 from its generally planar state along its length to form a structure having a plurality of voids 51 can also be used. Thus, the sheet member 6 of Figure 7 forms an integral agent reservoir housing and skin penetrating member.

Like the integral housing/skin penetrating member of Figure 7, Figure 21 also shows an integral incompressible reservoir housing and skin penetrating member designated 2'. Each of the sheet members 106 has a pair of holes 102, 103, through which bolts 105 are inserted. Spacers (e.g., hollow cylindrical members or washers) 107 are positioned between the sheet members 106 to form voids 127 therebetween. The spaced sheet members 106 are held together as a unit by securing nuts 104 on the ends of bolts 105, or using other known fasteners. As in the Figure 3 device, the voids 127 can be filled with a gel material adapted to contain the beneficial

agent to be delivered or to receive the body analyte to be sampled. The individual sheet members 106, which are oriented roughly perpendicularly to the surface of the skin, are composed of a metal which is substantially incompressible in a direction normal to the skin surface. Thus, a hold-down force applied to the top/skin distal edges of sheet members 106 by an adhesive overlay 3 (not shown in Figure 21), does not cause the sheet members to significantly compress in a direction normal to the skin surface.

The surface of housing 15 which contacts the skin distal side/edge of sheet member 6 is generally shown as flat (i.e., planar) in Figures 3 and 14. Most preferably however, the surface of housing 15 which contacts the sheet member 6 has a convex or curved (e.g., domed or cylindrically shaped) surface 54 as best shown in Figure 10. The radius of curvature of the convex or cylindrically shaped surface 54 is preferably at least about 5 cm, more preferably at least about 10 cm.

Figure 11 illustrates an alternate embodiment of the incompressible reservoir housing 15. In this embodiment, housing 15 is comprised of a plurality of strips which have a wavy (e.g., sinusoidal) shape and are oriented perpendicularly with respect to the plane of sheet member 6. Sheet member 6 has the same configuration shown in Figure 5 with openings 8 therein and associated microprotrusions 4 (not shown in Figure 11). The strips 91, 93 are preferably fixed together at their contact points 95 such as by welding in the case where the sheets 91, 93 are composed of metal or plastic. The configuration of the adjacent strips 91, 93 creates voids 97 therebetween for containing an appropriate reservoir material. Thus, the height of strips 91 and 93 will be governed in part by the volume, and hence the thickness, of the reservoir material loaded into voids 97.

Figure 12, illustrates yet another embodiment of incompressible reservoir housing 15. In this embodiment, housing 15 is comprised of a corrugated sheet 101. Corrugated sheet 101 is adapted to contact the skin distal side of sheet member 6. If necessary, a cover sheet (not shown in Figure 12) covering the skin distal side of corrugated sheet 101, or rails (also

not shown in Figure 12) along the side edges of corrugated sheet 101, can be used to provide additional incompressibility and/or rigidity to prevent any tendency for the sheet 101 to bend or fold along the corrugation folds when a hold-down force is applied to the skin distal side of sheet 101. Optionally, corrugated sheet 101 may have a plurality of openings (not shown in Figure 10) therein, thereby making it possible for agent to move through the corrugated sheet 101. The size and number of the openings may vary as long as the structural integrity and incompressibility of the corrugated sheet 101 is not compromised. The openings in the sheet 101 make it possible to place additional reservoir material into the voids 104 adjacent to the skin distal side of sheet 101. As in the other embodiments, a reservoir material can be loaded into the voids 103 formed between the corrugations and the underlying sheet member 6.

Figure 13 discloses an alternate embodiment of a corrugated sheet 101 in which the corrugation folds are not all parallel to one another. Similar to the device of Figure 12, the Figure 13 device can also be provided, if necessary, with a covering sheet over the skin distal side of corrugated sheet 101, or alternatively with an annular rail surrounding corrugated sheet 101, in order to enhance the structural incompressibility of corrugated sheet 101. Still further as in the Figure 12 device, the Figure 13 device can be provided with a plurality of openings (not shown in Figure 13) in the corrugated sheet 101 in order to allow agent delivery therethrough. Such openings make it possible to utilize voids 104 to contain agent reservoir material.

Yet another embodiment of the reservoir housing 15, illustrated in Figure 14, comprises a flexible, porous yet substantially incompressible material such as porous sintered high density polyethylene. Such porous sintered high density polyethylenes typically have a void volume in the range of about 10 to 60%, and more preferably about 30 to 40%. A liquid solution, a gel or other semi-solid agent reservoir material can easily be introduced using known pumping techniques into the voids of such sintered porous

materials. An example is Porex ® sintered porous high density polyethylene sold by Porex Technologies of Fairburn, G.A.

The microprotrusions or microblades 4 are generally formed from a single piece of material and are sufficiently sharp and long for penetrating at least the stratum corneum of the skin. In one embodiment, the microprotrusions 4 and the sheet member 6 are essentially impermeable or are impermeable to the passage of an agent. The width of each microprotrusion can be any of a range of widths. The width of the microprotrusion at the intersection of the microprotrusion and the body surface after the microprotrusion array has been inserted is typically at least about 25 μm. The required length of the blades is subject to variation of the body surface being penetrated and corresponds to at least the natural thickness of the stratum corneum, for one of the principal features of the invention is that the microprotrusions are to penetrate at least through the stratum corneum and into the epidermis. Usually, the microprotrusions will have a length and configuration which achieves a depth of penetration of about 25 μm to about 400 μm, with the depth of penetration for most applications being between about 50 μm to about 200 μm. The microprotrusions 4 can have slanted (i.e., angled) leading edges 64 (Figure 5) to further reduce the insertion force required to press the microprotrusions into the skin tissue. The leading edges of each microprotrusion 4 can all be the same angle or can be at different angles suitable for penetrating the skin. Alternatively, the leading edge of each microprotrusion can be curved having, for example, a convex or concave shape or be divided into any number of angled segments such as the first segment being relatively steep with respect to vertical and the second segment being more gradually angled with respect to vertical.

The sheet member 6 can be produced with a photolithography process followed by a chemical etching process followed by a micro-punching operation as disclosed in WO 97/48440. The embodiment of sheet member 6 illustrated in Figure 7 requires an additional step of forming the

planar sheet member 6 into the desired void-defining shape (i.e., spiral, serpentine, concentric circles, etc.). This can be accomplished using well-known metal sheet bending, rolling, folding and/or shaping techniques.

Generally, the microprotrusions 4 are at an angle of about 90° to the surface 48 (Figure 5) of the sheet member 6 after being punched, but they can be disposed at any angle forward or backward from the perpendicular position that will facilitate penetration of the stratum corneum.

The sheet member 6 and microprotrusions 4 can be made from materials that have sufficient strength and manufacturability to produce microprotrusions, such as, glasses, ceramics, rigid polymers, reinforced (e.g., carbon fiber reinforced) polymers, metals and metal alloys. Examples of metals and metal alloys include but are not limited to stainless steel, iron, steel, tin, zinc, copper, gold, platinum, aluminum, germanium, zirconium, titanium and titanium alloys. Each of the sheet member and microprotrusions can have a thin layer of gold, platinum, iridium, titanium, or rhodium plating. Examples of glasses include silicas and devitrified glasses such as "PHOTOCERAM" available from Corning in Corning, NY. Examples of polymers include but are not limited to polystyrene, polymethylmethacrylate, polypropylene, polyethylene, "BAKELITE", cellulose acetate, ethylcellulose, styrene/acrylonitrile copolymers, stryrene/butadiene copolymers, acrylonitrile/butadiene/styrene (ABS) copolymers, polyvinyl chloride and acrylic acid polymers including polyacrylates and polymethacrylates.

The number of microprotrusions 4 and openings 8 of any of the embodiments of the sheet member 6 is variable with respect to the desired flux rate, agent being sampled or delivered, delivery or sampling device used (i.e., electrotransport, passive, osmotic, pressure driven, etc.), and other factors as will be evident to one of ordinary skill in the art.

An optional connecting medium (not shown) can be predisposed on the skin contacting side 48 of the sheet member 6 having the configuration

shown in Figures 3-5 as taught in WO 98/28037. The connecting medium, if used, acts as a conduit for the agent and acts as a bridge between the agent containing or collecting reservoir and the skin, thus allowing an agent to be transported unhindered therethrough.

One type of transdermal delivery/sampling device, which can be used with the present invention relies on the application of an electric current across the body surface or "electrotransport". It will be appreciated by those working in the field that the present invention can be used in conjunction with a wide variety of electrotransport systems, as the invention is not limited in any way in this regard. For examples of electrotransport systems, reference may be had to U.S. Patent Nos. 5,147,296 to Theeuwes et al., 5,080,646 to Theeuwes et al., 5,169,382 to Theeuwes et al., 5,423,739 to Phipps et al., 5,385,543 to Haak et al., 5,310,404 to Gyory et al., and 5,169,383 to Gyory et al., of which any of the disclosed electrotransport systems can be used with the present invention.

Figures 15-19 illustrate a representative electrotransport delivery/sampling device 10 that may be used in conjunction with a housing 15 and a skin penetrating device 2 in accordance with the present invention. Device 10 comprises an upper housing 16, a circuit board assembly 18, a lower housing 20, donor electrode 22, counter electrode 24, donor reservoir 27, counter reservoir 28 and skin-compatible adhesive 30. Upper housing 16 has lateral wings 31 which assist in holding device 10 on a patient's skin. Printed circuit board assembly 18 comprises an integrated circuit 19 coupled to discrete components 40 and battery 32. Circuit board assembly 18 is attached to housing 16 by posts 33 (only one shown in Figure 17) passing through openings 13a and 13b, the ends of the posts being heated/melted in order to heat stake the circuit board assembly 18 to the housing 16. Lower housing 20 is attached to the upper housing 16 by means of adhesive layer 30, the upper surface 34 of adhesive layer 30 being adhered to both lower housing 20 and upper housing 16 including the bottom surfaces of wings 31. Shown (partially) on the underside of circuit

board assembly 18 is a button cell battery 32. Other types of batteries may also be employed to power device 10 depending on the need.

The incompressible reservoir housing 15 of the present invention is sized and shaped to fit snugly within depression 25' in lower housing 20. The donor electrode 22 also fits within depression 25 adjacent the skin distal surface of reservoir housing 15. In this embodiment, it is important that electrode 22 also be comprised of substantially incompressible material such as a metallic foil. A sheet member 6 having a plurality of microprotrusions 4, similar to that shown in Figure 5 is positioned adjacent the skin proximal surface of reservoir housing 15. Thus, when the device 10 is placed on the skin of the patient, the microprotrusions 4 extend downwardly and are adapted to pierce the outermost layer of the skin of the patient as best shown in Figures 17-19. The lower housing 20 is comprised of a non-stretchable, molded material such as polypropylene. The combination of lower housing 20 with the depression 25' surrounding device 2 in combination with the adhesive layer 30, comprise another example of a means for securing the housing 15, and the skin penetrating member 2 with the microprotrusions 4, on the skin of the patient.

The device 10 is generally comprised of battery 32, electronic circuitry 19,40, electrodes 22,24, counter reservoir 28, support member 15 housing donor reservoir 27, and skin penetrating device 2, all of which are integrated into a self-contained unit. Electrodes 22,24 and reservoirs 27,28 are retained by lower housing 20. The outputs (not shown in Figure 15) of the circuit board assembly 18 make electrical contact with the electrodes 24 and 22 through openings 23,23' in the depressions 25,25' formed in lower housing 20, by means of electrically conductive adhesive strips 42,42'. Electrodes 22 and 24, in turn, are in direct mechanical and electrical contact with the top sides 44',44 of reservoirs 27 and 28. The bottom side 46 of counter reservoir 28 contacts the patient's skin through the opening 29 in

adhesive layer 30. The bottom side 46' of donor reservoir 27 contacts the patient's skin through the plurality of openings 8 in the skin penetrating device 2 as best shown in Figure 3. The agent in donor reservoir 27 is typically in the form of a solution, most preferably an aqueous solution, which solution is contained in a solid matrix material such as a hydrophilic polymer matrix (e.g., a hydrogel) which allows free mobility of the agent therethrough. The reservoir matrix material fills the voids between the cross members 5 and the openings 8 in the sheet 6 (not shown in Figure 15) such that the agent reservoir is in contact with the body surface as can best be seen in Figure 3. As discussed above, a connecting medium can be placed as a layer on the skin-proximal side of sheet 6, with the microblades 4 passing therethrough. The optional connecting medium provides a more consistent agent flow pathway between the donor reservoir 27 and the skin. Typically the agent is present initially in both the reservoir and the connecting medium because of diffusion or because the reservoir and connecting medium are the same material.

The device 10 adheres to the patient's body surface (e.g., skin) by means of a peripheral adhesive layer 30 (which has upper adhesive side 34 and body-contacting adhesive side 36) and, optionally, anchoring elements on the device 2 of any of the embodiments discussed herein. Further, optionally, the connecting medium 65 can be tacky or adhesive for assisting in maintaining interface contact with the skin. The adhesive side 36 covers the entire underneath side of the device 10 except where the device 2 and counter electrode reservoir 28 are located. The adhesive side 36 has adhesive properties which assures that the device 10 remains in place on the body during normal user activity, and yet permits reasonable removal after the predetermined (e.g., 24-hour) wear period. Upper adhesive side 34 adheres to lower housing 20 and retains the electrodes and agent reservoirs within housing depression 25, 25' as well as retains device 2 to lower housing 20 and lower housing 20 to upper housing 16.

In one embodiment of the agent delivery/sampling device there is a

release liner (not shown) on the device 10 for maintaining the integrity of adhesive layer 30 when the device is not in use. In use, the release liner is stripped from the device before the device is applied to the skin. Device 10 also has a push button switch 12, which when pressed turns the device 10 on which is made apparent to the user by means of LED 14 becoming lit. Agent is delivered through the patient's skin (e.g., on the arm) by electrotransport over a predetermined delivery interval.

In other embodiments of the present invention, passive transdermal delivery or sampling devices are used with housing 15 predisposed on the top (i.e., skin distal) surface of the member 6. It will be appreciated by those working in the field that the present invention can be used in conjunction with a wide variety of passive transdermal systems, as the invention is not limited in this regard. For examples of passive systems, reference may be had to, but not limited to, U.S. Patent Nos. 4,379,454 to Campbell, et al., 4,588,580 to Gale et al., 4,832,953 to Campbell et al., 4,698,062 to Gale et al., 4,867,982 to Campbell et al., and 5,268,209 to Hunt et al., of which any of the disclosed systems can be used with the present invention. One example of a passive transdermal delivery/sampling device is illustrated in Figure 20. Housing 15 having the edges of sheet member 6 embedded in the outer annular wall 53 thereof is housed in a foam pad 57 which can be applied (e.g., adhered) to the body surface. The edges of sheet member 6 need not be embedded in the outer annular wall, as the sheet member 6 can be attached to the housing 15 as described in the previous embodiments. Extending across annular wall 53 and cross-member 5 is a top 59. Top 59 is fixedly attached at either end to outer annual wall 53 and foam pad 57. The skin proximal surface of foam pad 57 is coated with adhesive and adheres to the skin. Thus, the combination of foam pad 57 and top 59 comprise yet another means for securing reservoir housing 15 to a patient's skin. The passive delivery/sampling device has a peripheral adhesive on the body-contacting surface of foam pad 57 and an adhesive interface gel (not shown) on the body-contacting side of the member 2.

It will be appreciated by those working in the field that the present invention can also be used in conjunction with a wide variety of osmotic and pressure driven systems, as the invention is not limited to a particular device in this regard. For examples of osmotic and pressure driven devices, reference may be had to U.S. Patent Nos. 4,340,480 to Eckenhoff, 4,655,766 to Theeuwes et al., 4,753,651 to Eckenhoff, 5,279,544 to Gross et al., 4,655,766 to Theeuwes, 5,242,406 to Gross et al., and 4,753,651 to Eckenhoff any of which can be used with the present invention.

This invention has utility in connection with the delivery of agents within any of the broad class of drugs normally delivered through body surfaces and membranes, including skin. In general, this includes drugs in all of the major therapeutic areas. The invention is also useful in the transdermal delivery of proteins, peptides and fragments thereof, whether naturally occurring, chemically synthesized or recombinantly produced. The invention may additionally be used in conjunction with the delivery of vaccines, nucleotidic drugs, including oligonucleotide drugs, polynucleotide drugs, and genes. These substances typically have a molecular weight of at least about 300 daltons, and more typically have a molecular weight of at least about 300 to 40,000 daltons. As mentioned, the device 2 of the present invention can also be used with sampling devices including, but not limited to, reverse electrotransport (i.e., reverse iontophoresis and/or reverse electroosmosis in the case of sampling uncharged materials such as glucose), osmosis, and passive diffusion. For example, reference may be had to U.S. Patent Nos. 4,756,314 to Eckenhoff et al., 5,438,984 to Schoendorfer, 5,279,543 to Glikfeld et al., and 5,362,307 to Guy et al. The invention will be further illustrated by the following specific examples.

Example 1

Hairless guinea pigs were anesthetized with ketamine/xylazine. The skin was washed with soap and water, dried and then wiped gently with an isopropyl alcohol pads. The skin of the animals was manually bidirectionally

stretched and a foam housing (outer diameter of 3.8 cm , inner diameter of 1.6 cm and thickness of 1.6 mm) was applied to the stretched skin site. A microprotrusion array (a stainless steel sheet having a plurality of openings therein, a thickness of 25 μm, a microprotrusion length of 500 μm, a microprotrusion density of 72 microprotrusions/cm^2, and a skin-contact area of 2 cm^2 (circular shape, 1.6 cm diameter) was inserted into the center of the foam housing, microprotrusion side down. A hard plastic button (1.6 cm diameter) was placed on the skin distal side of the microprotrusion array. The microprotrusions were forced into the skin by folding the skin where the housing and microprotrusion array had been placed. The thumb was placed over the button and the index finger was below the flap of skin and directly below the microprotrusion array. Manual pressure (approximately 2 kg/cm^2) was applied for approximately 10 seconds. Each application type was performed in triplicate at every time point.

For the pretreatment, the microprotrusion array was removed after manual application and the release liner removed from the foam housing. The compartment was filled with either 350 μL of a gel comprised of an aqueous phosphate buffered saline solution containing 3% hydroxyethylcellulose (HEC gel) or a gel comprised of an aqueous phosphate buffered saline solution containing 23% polyvinylalcohol (PVOH gel). A release liner top (3.8 cm diameter) was adhered to the top of the foam housing. The animals were wrapped with Vetrap™ adhesive tape and allowed to recover until the end of their specified wearing time.

For the in situ treatment, the microprotrusion array was left in place after manual application. The release liner was removed from the foam housing and a hydrophilic porous sintered high density polyethylene matrix (2 cm^2 area, 1.6 cm diameter and a thickness of 1.6 mm (HDPE matrix) was placed against the skin distal side of the microprotrusion array. Phosphate buffered saline solution was pipetted into the compartment (250 μL). A release liner top was adhered to the top of the foam housing. The combination of the foam housing adhered to the skin and the release liner

top adhered to the foam housing comprised a hold down means for securing the HDPE matrix securely against the microprotrusion array. The animals were wrapped with adhesive tape and allowed to recover until the end of their specified wearing time.

At the end of the wearing times (0, 0.5, 1, 2, and 24 hours), the wrapping and systems were removed. Excess gel or liquid was wiped away with a gauze pad. A cotton swab was imbibed with India ink (Higgins® Eternal Black India ink) until saturated. The treated sites were lightly stretched by hand and the dye liberally rubbed into the sites. The dye was applied in a circular motion, applying in two opposing directions for approximately 15 seconds. The excess dye was wiped off with a gauze pad. Isopropyl alcohol pads were then used to remove any dye from the skin until only the dyed microcuts/pathways created by the microprotrusion arrays were visible. Photographs were taken of the sites with a video scope. Subsequently, the animals were euthanized and the skin sites removed and frozen. Each frozen skin site was biopsied with an 8 mm biopsy punch. Biopsies were mounted onto a cryostat chuck and sectioned parallel to surface, first section at 20 μm, remainder at 50 μm. Thereafter, the individual skin sections were mounted onto microscope slides and individually dyed holes counted in each slice. From these data, and from the density of microprotrusions in the microprotrusion arrays, the percent of pathways that were dyed in a particular skin section can be calculated and plotted as a function of depth. Each data point represents the mean of three determinations with its associated standard error. The average depth at which 16%, 50% and 84% of the pathways are dyed (D_{16}, D_{50}, D_{84}) can also be extrapolated as well as their associated standard error.

Penetration of the dye into the skin is an indication that the microprotrusions have penetrated the skin and that the pathways created are open. Therefore, this technique was used to evaluate penetration of the microprotrusions into the skin as well as pathway collapse as a function of time after application of the microprotrusion array. Figure 22 shows the

percentage of pathways dyed as a function of depth (i.e., depth as measured from the skin's outer surface) one hour after application of the microprotrusion array. Figure 22 shows that when the microprotrusion array is left in situ, which is achieved with the use of the HDPE matrix and the securing overlay, the pathways are more open and are deeper than when microprotrusion array is applied and then removed from the skin (ie, use of the microprotrusion array as a pretreatment). This indicates that the HDPE matrix and the securing overlay are capable of maintaining the microprotrusions in skin-piercing relation to the skin and thereby delaying pathway closure.

The kinetics of pathway collapse is illustrated in Figure 23 by the plot of D_{50} as a function of time after application of the microprotrusion array. These data show that pathway collapse occurs quickly (e.g., within the first hour) following pretreatment application of the microprotrusion array. Pathway collapse is inhibited when the microprotrusion array is left in situ, which is achieved with the use of the HDPE matrix and the securing overlay. This indicates that the HDPE matrix and the securing overlay maintain the microprojections in piercing relation to the skin, at a depth of more than 150 μm, for at least 2 hours. Figure 24 shows the same kinetics obtained with the HDPE matrix for up to a 24 hour wearing time. After 24 hours, 50% of the pathways (D_{50}) are still open to a depth of about 150 μm.

It will be appreciated by those of ordinary skill in the art that the invention can be embodied in other specific forms without departing from the spirit or essential character thereof. The presently disclosed embodiments are therefore considered in all respects to be illustrative and not restrictive. The scope of the invention is indicated by the appended claims rather than the foregoing description, and all changes which come within the meaning and range of equivalents thereof are intended to be embraced therein.

Claims:

1. A device (2) for use in introducing or withdrawing an agent through a body surface, comprising a body surface piercing member (6) having a plurality of microprotrusions (4) extending from a body surface proximal portion (48) of the member, the microprotrusions (4) being adapted to pierce the body surface to a depth of up to about 500 μm, and

a reservoir (27) for the agent to be introduced or withdrawn, the reservoir (27) being adjacent the piercing member (6) and in agent-transmitting relation with the pierced body surface, and a securing member (3) for securing the device (2) to the body surface, the device (2) being characterized by:

a housing (15) for containing the agent reservoir (27), the housing (15)having a compressibility, in a direction normal to the body surface, of less than about 250 μm.

2. The device of claim 1, wherein the housing (15) contacts and extends across the entire body distal portion (48) of the piercing member (6).

3. The device of claim 1, wherein the securing member (3) is selected from the group consisting of an adhesive overlay, a tape and a strap.

4. The device of claim 1, wherein the housing (15) has a compressibilty of less than about 50 μm.

5. The device of claim 1, wherein the housing (15) is comprised of a material selected from the group consisting of porous sintered polymers, open cell polymeric foams, porous polymer sheets, polymer screens, woven polymeric fabrics, porous ceramics, and a corrugated polymer sheet.

6. The device of claim 1, wherein the housing (15)has sufficient flexibility to form a curved configuration in response to a hold down force applied by the securing member (3).

7. The device of claim 6, wherein the housing (15) is comprised of a material selected from the group consisting of porous sintered polymers, open cell polymeric foams, porous polymer sheets, polymer screens, woven polymeric fabrics and a corrugated polymer sheet.

8. The device of claim 3, wherein the securing member (3) comprises an adhesive.

9. The device of claim 8, wherein the adhesive is a skin contact adhesive.

10. The device of claim 1, wherein the housing (15) is comprised of a plurality of sections, each section being substantially non-flexible in response to a hold down force applied by the securing means, the sections being hingedly attached to one another.

11. The device of claim 1, wherein the housing (15) is comprised of porous sintered high density polyethylene.

12. The device of claim 1, wherein the housing (15) is comprised of open cell polyurethane foam.

13. The device of claim 1, wherein the housing (15) is comprised of open cell polyvinyl alcohol foam.

14. The device of claim 1, wherein the agent is a drug to be introduced into the body surface and the reservoir (27) is a drug reservoir.

15. The device of claim 14, wherein the drug reservoir (27) contains a transdermal drug formulation.

16. The device of claim 1, wherein the agent is a body analyte to be withdrawn from the body surface and the reservoir (27)is an analyte collection reservoir.

17. The device of claim 16, wherein the body analyte is glucose.

18. The device of claim 1, wherein the piercing member comprises a sheet (6) having a thickness of about 5 to 100 μm, the sheet (6) having a plurality of openings (8) therethrough, a body proximal surface (48) adapted to be placed against the body surface and said plurality of microprotrusions (4) extending from the body proximal surface (48).

19. The device of claim 18, wherein the sheet (6) is comprised of metal.

20. The device of claim 19 wherein the metal is selected from the group consisting of stainless steel and titanium.

21. The device of claim 1, wherein the piercing member comprises a sheet (6, 106)having a thickness of about 5 to 100 μm, the sheet (6, 106)having a body proximal edge (49), with said plurality of microprotrusions (4), adapted to be placed against said body surface.

22. The device of claim 21, wherein the sheet (6, 106) is comprised of metal.

23. The device of claim 22, wherein the metal is selected from the group consisting of stainless steel and titanium.

24. The device of claim 21, wherein the housing (15) comprises a plurality of said sheets (106).

25. The device of claim 1, wherein the microprotrusions (4) are maintained in piercing relation to the skin surface of an animal during normal movement thereof.

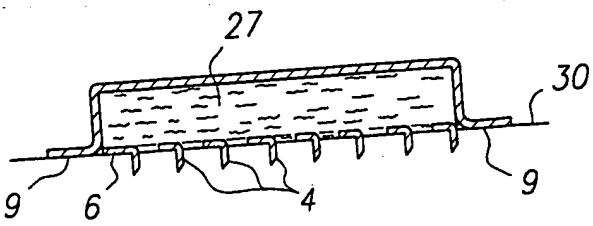


FIG. 1 PRIOR ART

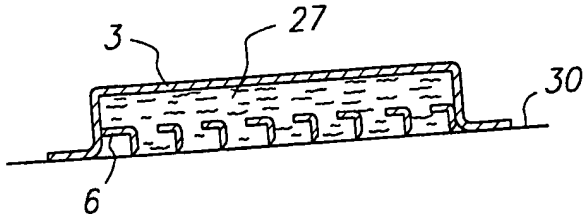


FIG. 2 PRIOR ART

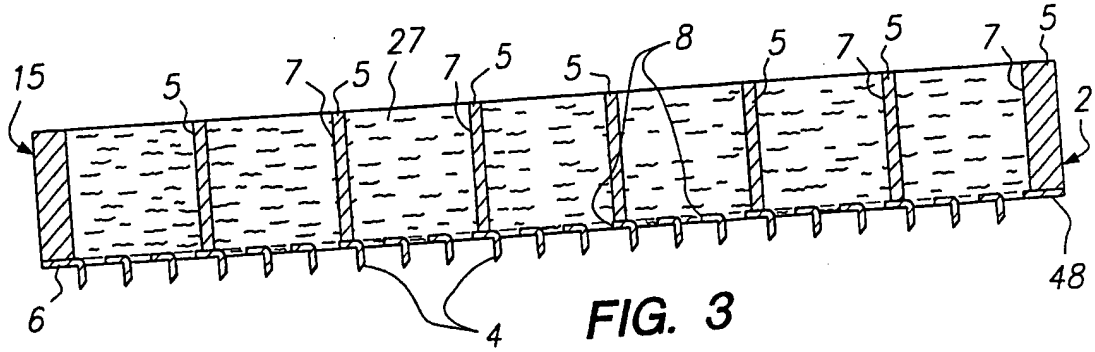


FIG. 3

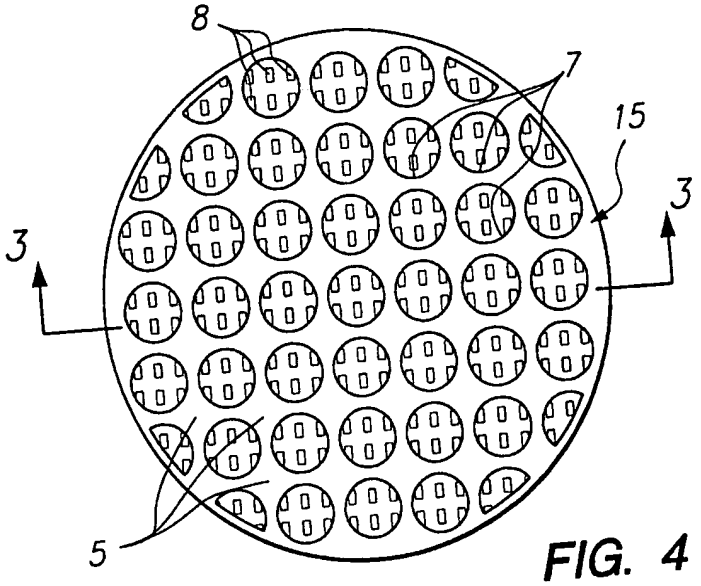


FIG. 4

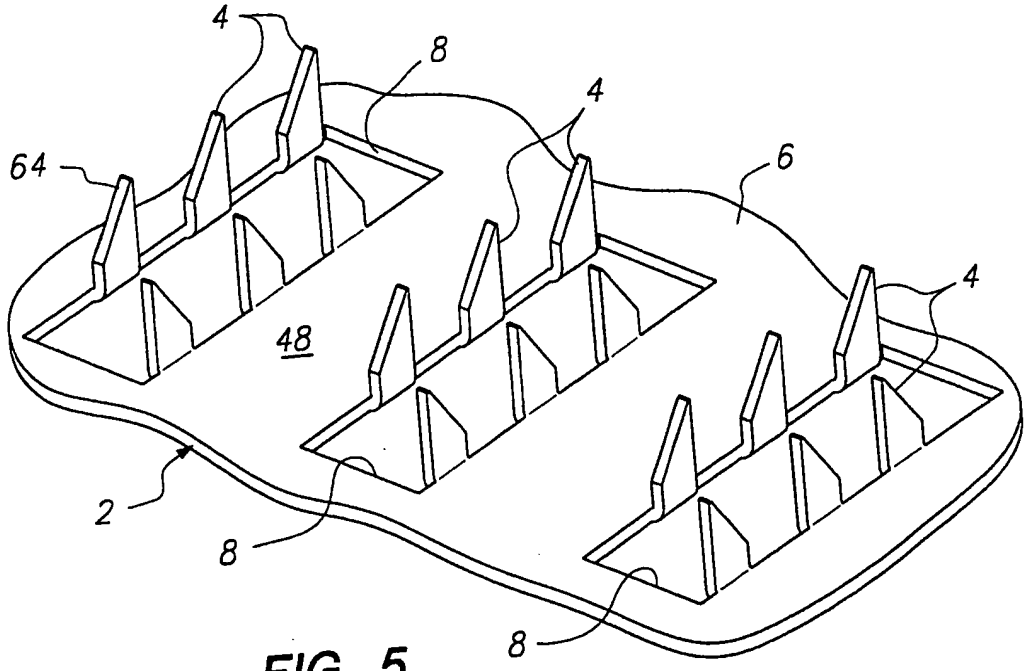


FIG. 5

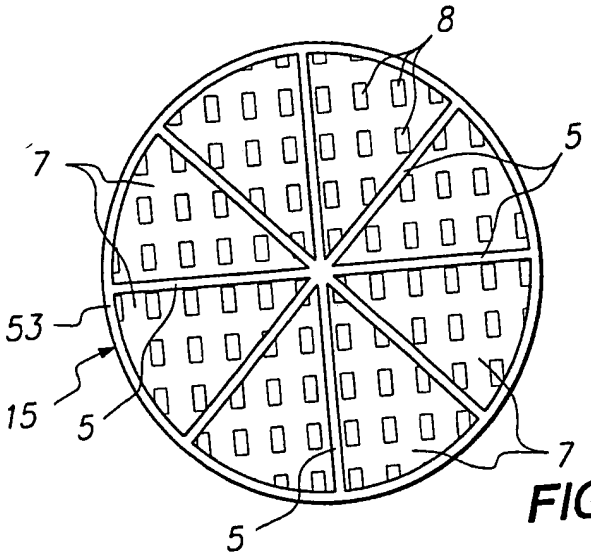


FIG. 6

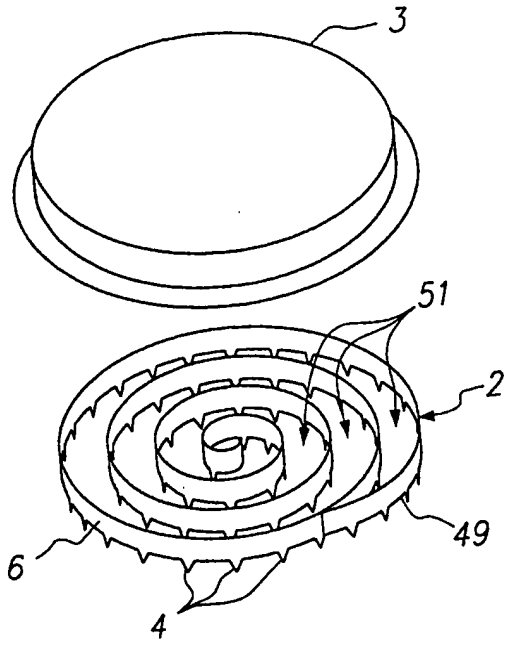


FIG. 7

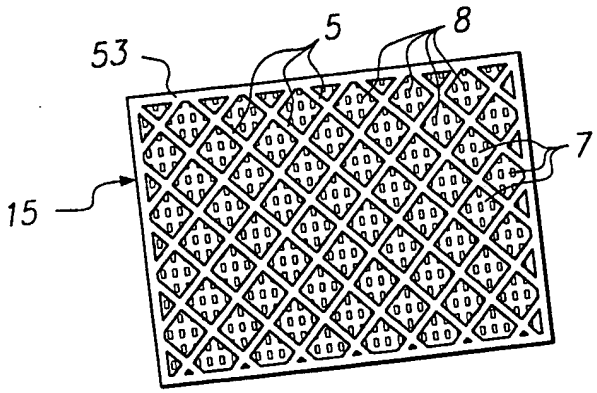
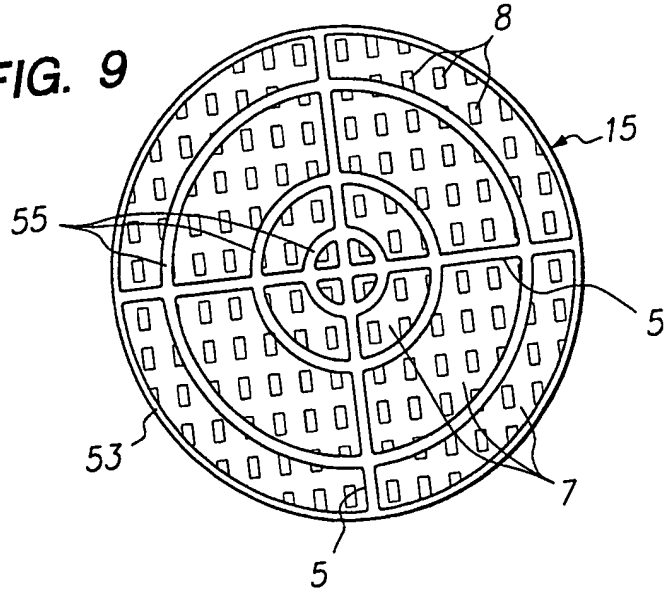


FIG. 8

FIG. 9



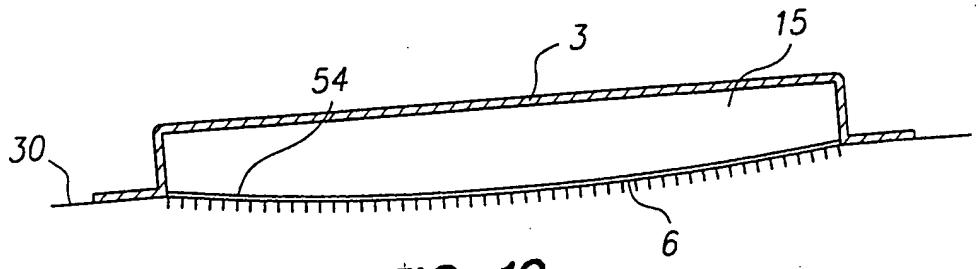


FIG. 10

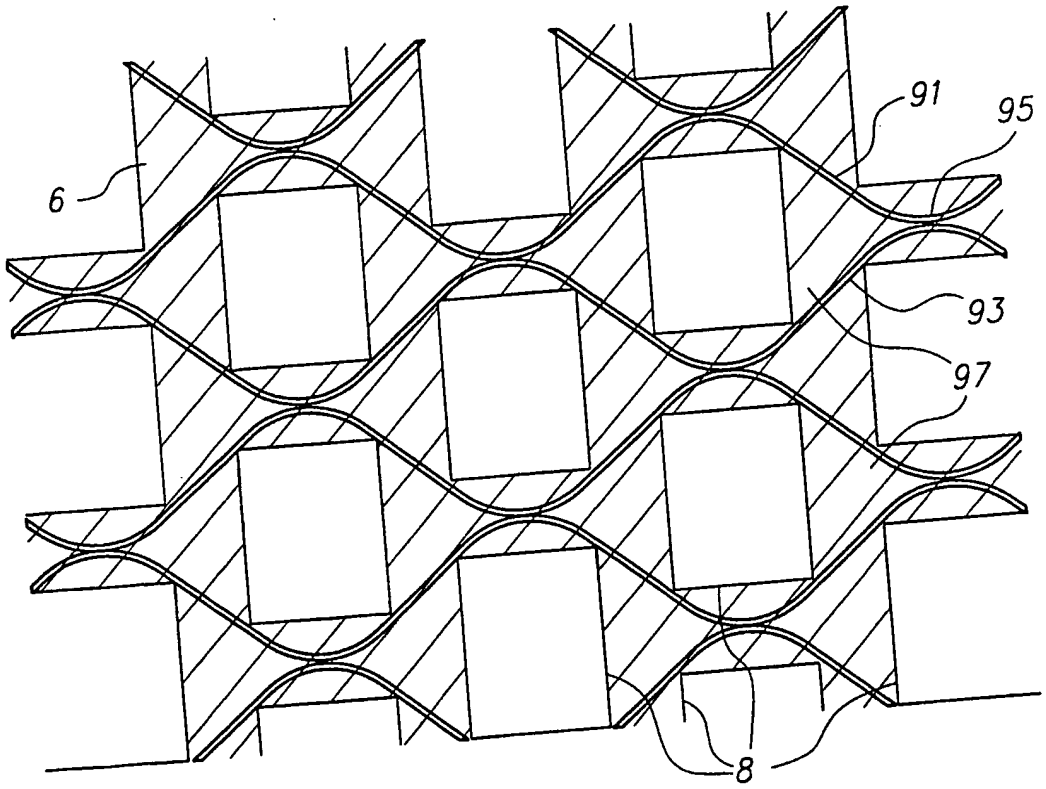


FIG. 11

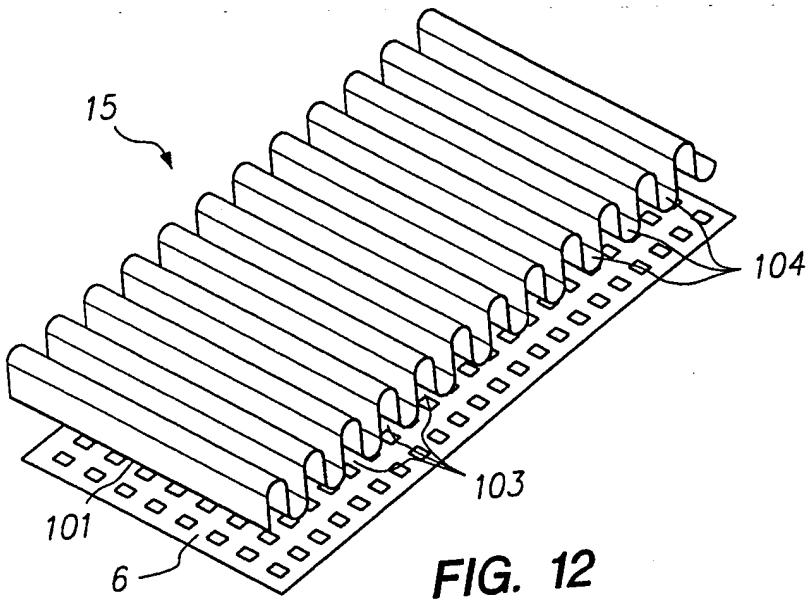


FIG. 12

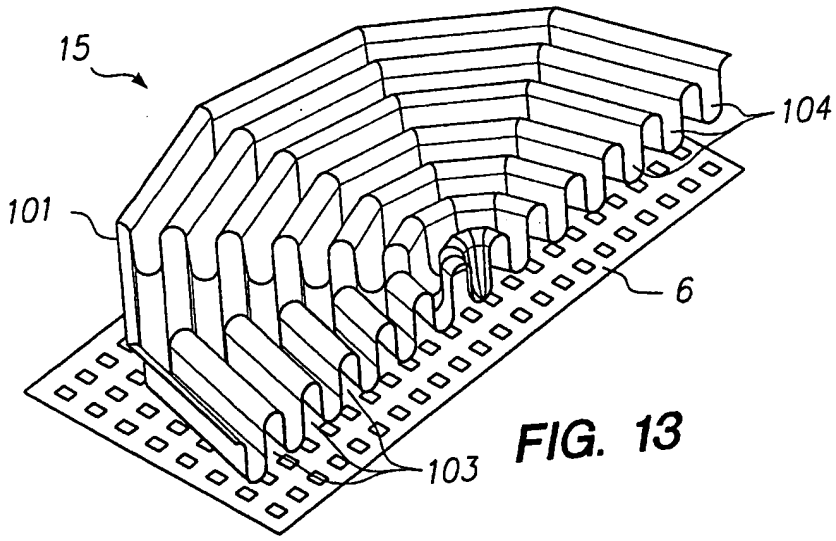


FIG. 13

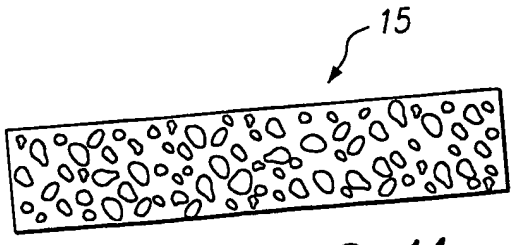


FIG. 14

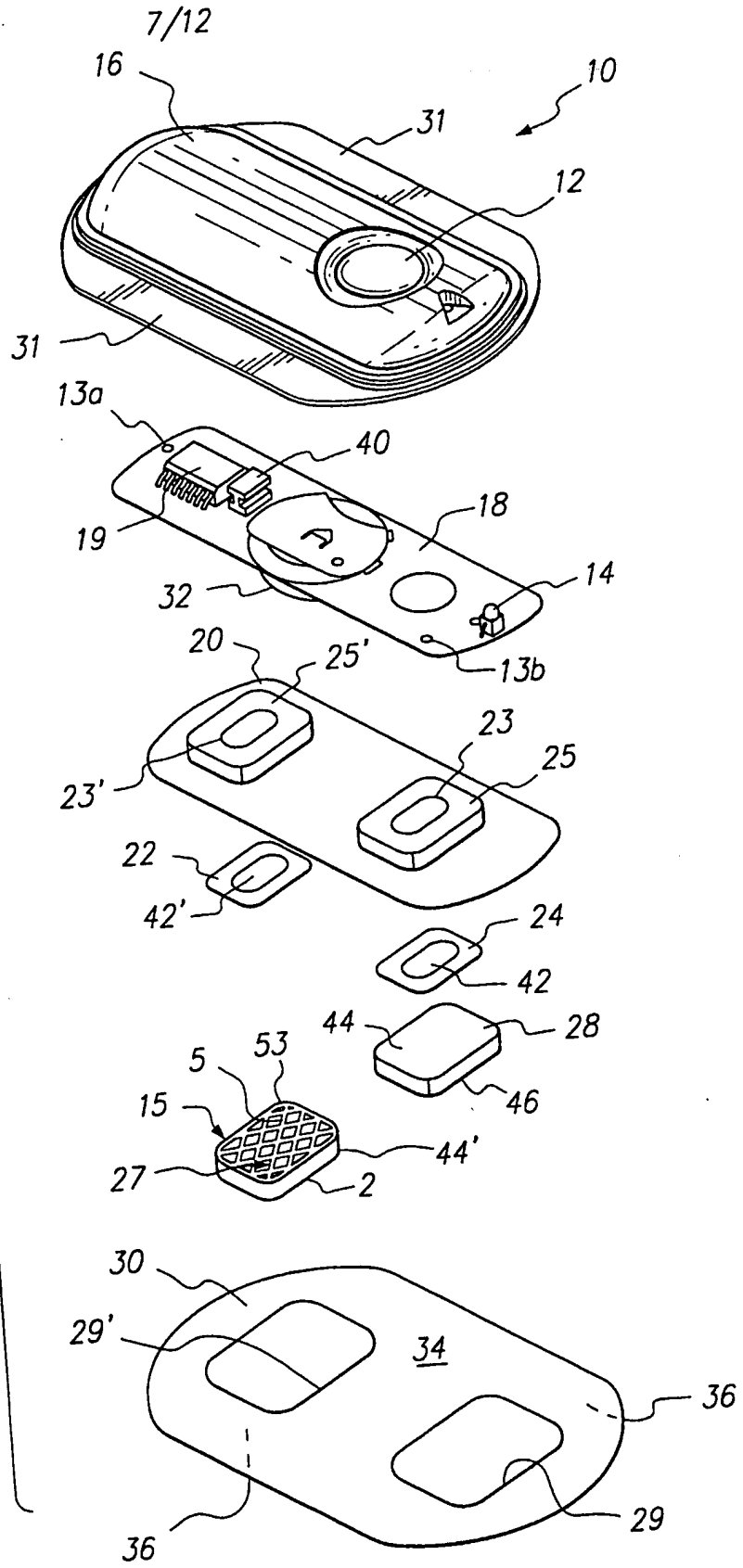

16
10
31
12
31
13a
40
18
19
14
32
13b
20
25'
23
23'
25
22
42'
24
42
44
28
5
53
46
15
44'
27
2
30
29'
34
36
36
29

FIG. 15

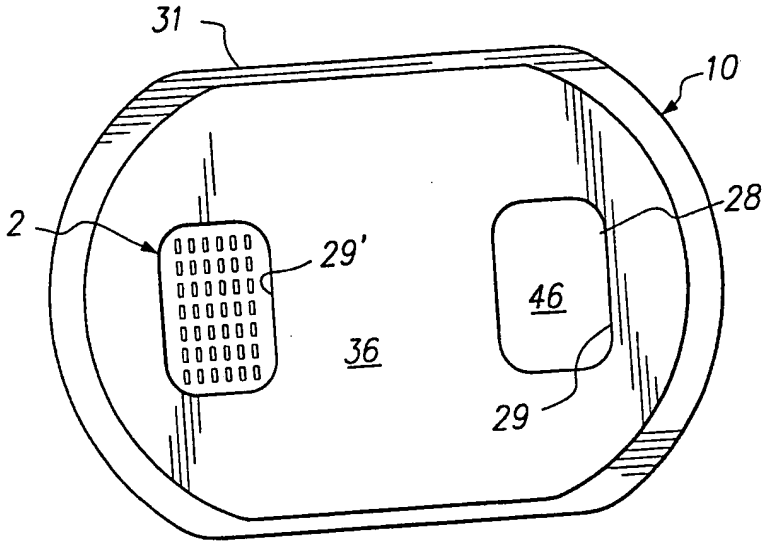


FIG. 16

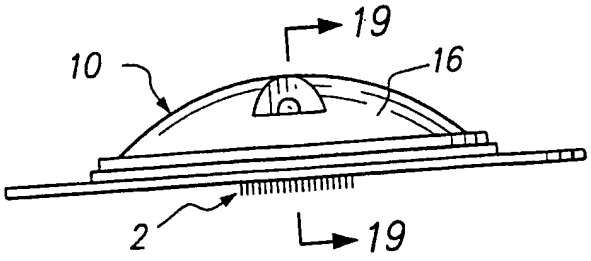


FIG. 17

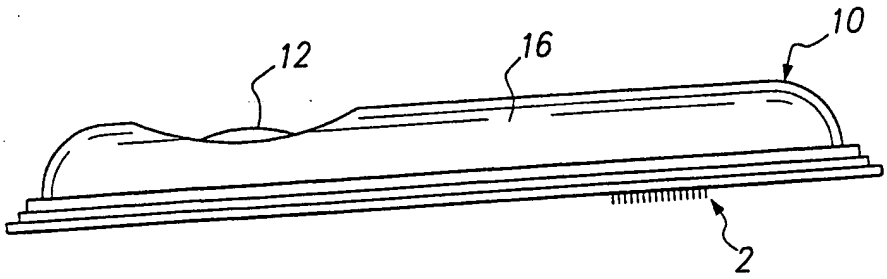


FIG. 18

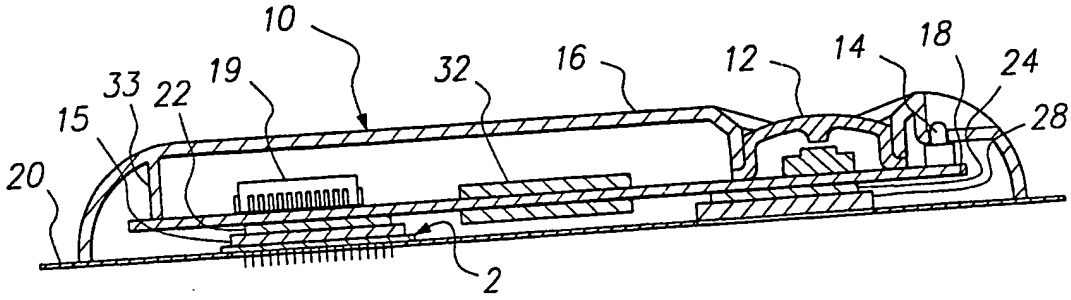


FIG. 19

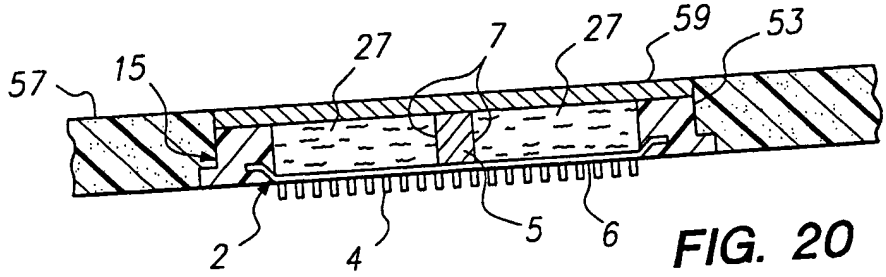


FIG. 20

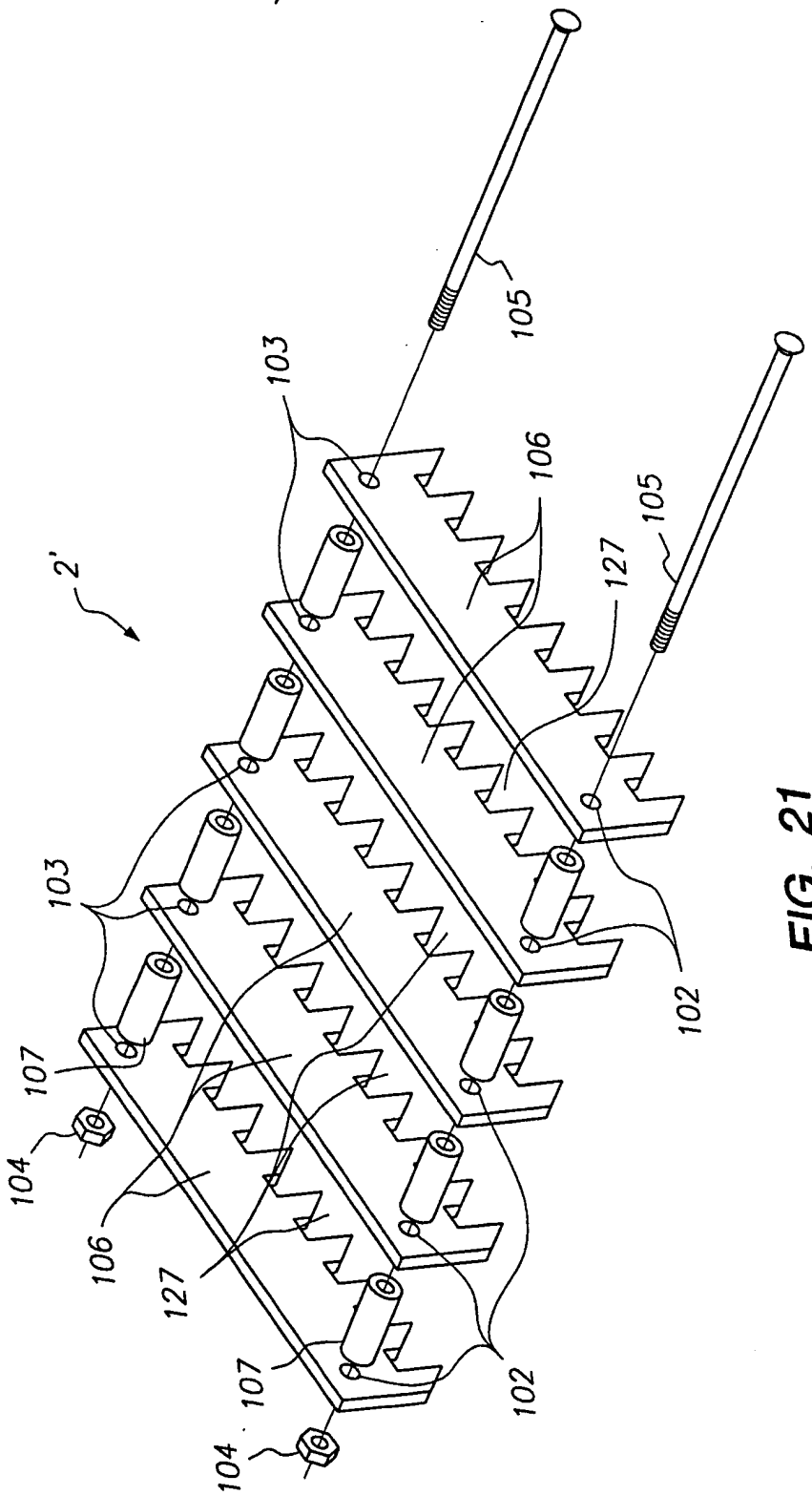


FIG. 21

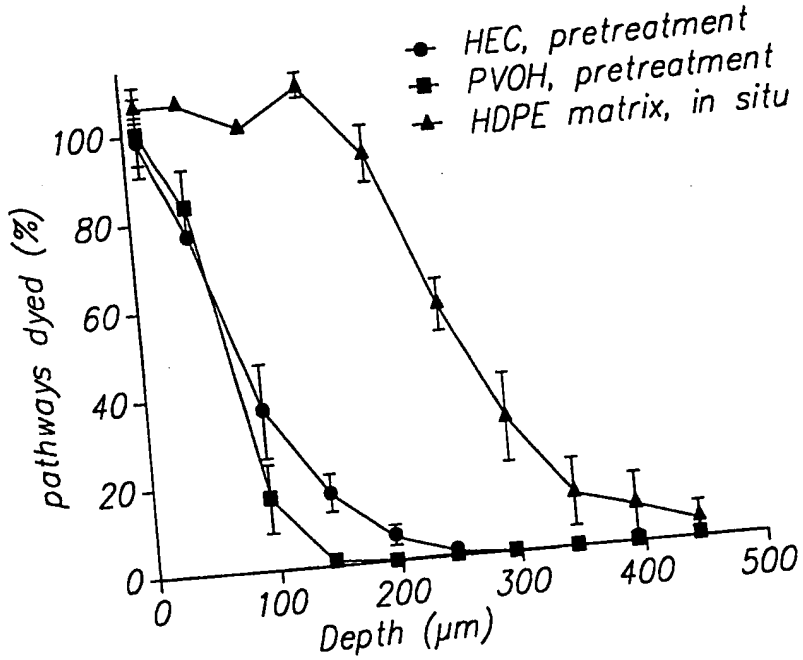

HEC, pretreatment
PVOH, pretreatment
HDPE matrix, in situ
pathways dyed (%)
0
20
40
60
80
100
0
100
200
300
400
500
Depth (μm)

FIG. 22

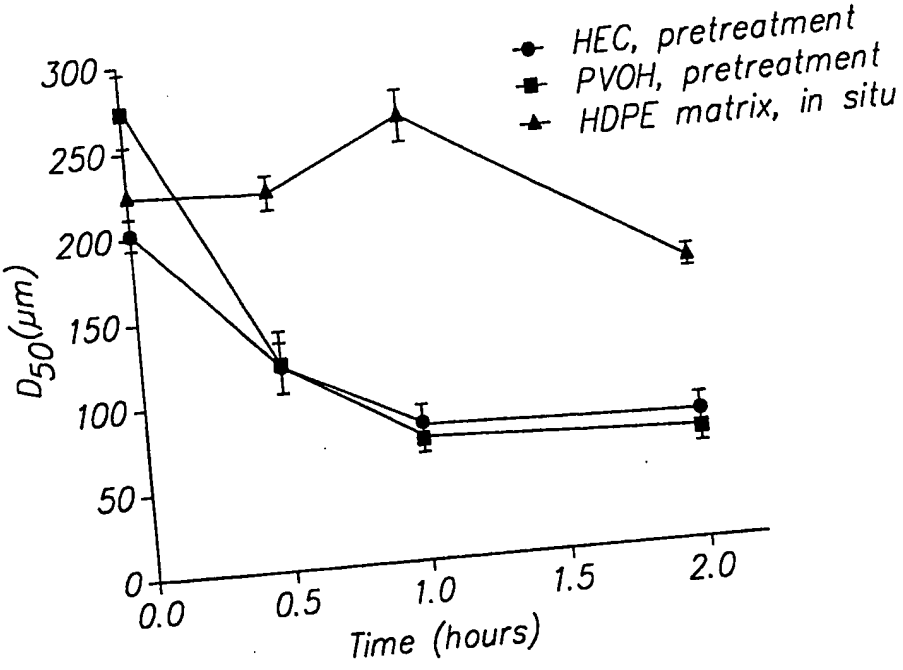

HEC, pretreatment
PVOH, pretreatment
HDPE matrix, in situ
D_{50}(μm)
0
50
100
150
200
250
300
0.0
0.5
1.0
1.5
2.0
Time (hours)

FIG. 23

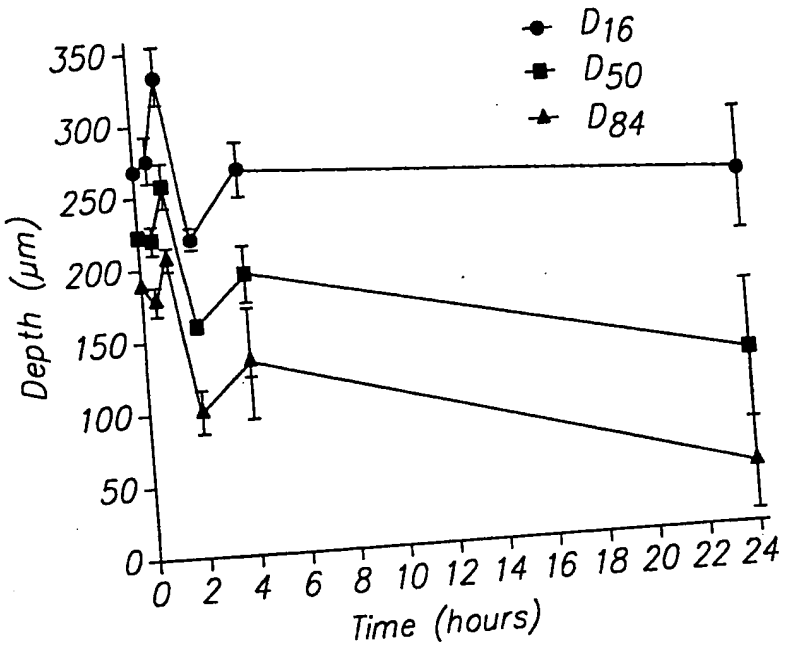

D16
D50
D84
350
300
250
200
150
100
50
0
Depth (μm)
0 2 4 6 8 10 12 14 16 18 20 22 24
Time (hours)

FIG. 24

INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/US 98/26203

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61M37/00 A61N1/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61M A61N A61K A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 17648 A (CIBA-GEIGY) 13 June 1996 see page 7, line 9 - page 11, line 2; figures	1,2,14, 15,25
A	GB 2 221 394 A (EILERTSEN) 7 February 1990 see page 3, line 9 - page 4, line 28; figures	1,3,9,14
A	US 3 964 482 A (GERSTEL) 22 June 1976 see column 7, line 22 - column 10, line 54; figures	1,2,6, 14,15
A	DE 195 25 607 A (BOEHRINGEN) 16 January 1997 see claims 1-13; figures	1,2,5,6, 14,15

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 April 1999	10/05/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Kousouretas, I

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INTERNATIONAL SEARCH REPORT

Int. ional Application No
PCT/US 98/26203

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 37256 A (SILICON MICRODEVICES) 28 November 1996 cited in the application see abstract; figures	1

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int ional Application No
PCT/US 98/26203

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WO 9637256 A	28-11-1996	AU 5869796 A	11-12-1996